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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/547,220	04/11/2000	Michael Brines	10165-006-999	4714

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JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/547,220	BRINES ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Prosecution is hereby reopened. The indicated allowability of claims 28-39 (suspensions 1/28/03; 12/2/03; 9/22/04) is *withdrawn* in view of the new rejections. The finality of the rejection of the last Office Action is *withdrawn* in view of the new grounds of rejection set forth below.

Status of Application, Amendments and/or Claims

The amendment filed 18 December 2002 has been entered in full. New claims 40-63 were added. Claims 28-63 are examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

The information disclosure statement(s)(IDS) filed 26 August 2004 was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits.

Withdrawn Objections And/Or Rejections

The rejection to claims 28-39 under 35 USC 112, first paragraph as set forth at pages 3-4 of the previous Office Action (22 October 2002) is *withdrawn* in view of the amendment and Applicant's arguments (18 December 2002).

The rejection to claims 28 and 34 under 35 USC 112, second paragraph as set forth at page 4 of the previous Office Action (22 October 2002) is *withdrawn* in view of Applicant's arguments (18 December 2002).

NEW REJECTIONS:

Claim Rejections - 35 USC § 112, First Paragraph, Scope of Enablement

Claims 33, 39, 45, 51, 57 and 63 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

"a method for treating cerebral ischemia....comprising peripherally administering .....**native erythropoietin, recombinant human erythropoietin or animal erythropoietin**.."

does not reasonably provide enablement for:

"a method for treating cerebral ischemia....comprising peripherally administering.....a **derivative thereof** (native erythropoietin, recombinant human erythropoietin or animal erythropoietin).."

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Derivatives of erythropoietins (EPO) can broadly encompass any type of mutein, variant, fragments, chemical modifications, analogs, etc. The scope of patent protection sought by Applicant as defined by the claims fails to bear a reasonable correlation with the scope of an enabling disclosure set forth in the specification because the

specification does not teach how to make and use derivatives of EPO that are effective to exert a neuroprotective effect upon peripheral administration and provides no assay to evaluate the function of any modified polypeptide. The instant specification fails to indicate that a representative number of structurally related compounds are disclosed and therefore, the artisan would not know the identity of a reasonable number of representative compounds falling within the scope of the instant claim and would not know how to make them.

In order to make a sequence variant, for example, with the reasonable assurance that it would have the desirable properties of the invention, the artisan would need to know which regions of the disclosed polypeptide are responsible for the interactions underlying its biological function(s). A vast number of derivatives would need to made and then screened for neuroprotection. Without sufficient guidance, the changes that can be made in the structure and still maintain sufficient activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly undue.

As is well recognized in the art, any modification (even a "conservative" substitution) to a critical structural region of a protein is likely to significantly alter its functional properties. It is known for nucleic acids as well as proteins, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases. The disclosure provides no guidance as to which regions of the protein would be tolerant of modification and which would not, and it provides no working example of any variant sequence, which would be within the claims. It is in no way predictable that randomly selected mutations, deletions, *etc.* in the disclosed sequence

would afford a protein having activity comparable to the one disclosed (neuroprotection). Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (Wells, 1990, Biochemistry 29:8509-8517). Applicant has provided no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein that are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions.

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims for "EPO derivatives thereof" and screen same for neuroprotection, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide neuroprotection, the absence of working examples directed to same, the complex nature of the invention and the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, First Paragraph, Written Description

Claims 33, 39, 45, 51, 57 and 63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant method requires the use of undisclosed derivatives of erythropoietin.

The specification provides adequate written description for native erythropoietin, recombinant human erythropoietin or animal erythropoietin but not derivatives thereof. There is insufficient descriptive support for EPO derivatives. The specification does not place any limit on the number of nucleotides substitutions, deletions, insertions and/or additions that may be made to EPO. There is insufficient descriptive support for the genus "derivatives of EPO".

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

With the exception of EPO, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptide and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or

simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only native erythropoietin, recombinant human erythropoietin or animal erythropoietin but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112, First Paragraph, Written Description, New Matter

Claims 40 and 46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The specification as originally filed does not provide support for the invention as now claimed: ".....without a **toxic** increase in hemoglobin concentration or hematocrit". Applicant's amendment, filed 18 December 2002, asserts that no new matter has been added and directs support to page 13, lines 24-26 and page 22, line 32-page 23, line 20 for the written description for the above-mentioned "limitations". The exact wording or connotation of the instant claims is not readily apparent from said sections.

The specification as filed does not provide a written description or set forth the metes and bounds of this "limitations". The instant claims now recite limitations which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as-filed.

Applicant is required to cancel the new matter in the response to this Office action. Alternatively, Applicant is invited to provide specific written support for the "limitations" indicated above or rely upon the limitations set forth in the specification as filed.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 28, 34, 40, 46, 52 and 58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 28, 34, 40, 46, 52 and 58 are indefinite because the claims must achieve the goal stated in the preamble. The instant claims do not have a step that clearly relates back to the preamble.

Claims 40 and 46 recite, "....**without a toxic increase in** hemoglobin concentration or **hematocrit**". Claims 52 and 58 recite, "....**without an increase in hematocrit**". Neither the specification nor the art provides unambiguous definitions for these terms (increase vs. toxic increase) such that the difference in scope between the two claims can be ascertained. The metes and bounds of the claims cannot be determined.

Claim Rejections - 35 USC § 102(b)

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 28-63 are rejected under 35 U.S.C. 102(b) as being anticipated by Igari *et al.,* US Patent 5,591,713.

Igari *et al.* teach a method of intravenously administering a pharmaceutical composition comprising recombinant erythropoietin (EPO) to humans, wherein said EPO is administered at dosages of 50,000 to 100,000 Units per administration (abstract; column 5, line 65-column 6, line 6; column 7, lines 41-50 and column 8, lines 41-65).

The dose taught by Igari *et al.* inherently has the effect recited in the claims. The EPO dosage administered, as taught by Igari *et al.,* inherently has a neuroprotective effect and is non-toxic (no increase in hemoglobin concentration or hematocrit). "Treating cerebral ischemia" and "for the treatment of stroke" are intended uses recited

in the instant claims and are not given patentable weight. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001) in which the Court found that preamble language in claims of patents directed to administration of anticancer drug are expressions of purposes and intended results, and as such are non-limiting, since language does not result in manipulative difference in steps of claims. It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. The instant claims do not identify a specific mammalian patient population (claims do not state that the mammal suffers from any condition). "Treating" can reasonably be broadly interpreted as encompassing prophylactic treatment in a healthy patient. Igari's teachings of administering erythropoietin do not teach against the intended use cited in the claims.

Claim Objections

Claims 40, 46, 52 and 58 are objected to because of the following informalities.

Claims 40/52 and 46/58 are objected to because the instant claims appear to read on the same scope. The instant claims comprise very similar steps, which raises the question of similar scope. If the claims are not of similar scope, Applicant is asked to specifically point in the specification, the patentable distinction between the claims.

Conclusion

Claims 28-63 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JOSEPH MURPHY
PATENT EXAMINER

RMD
5/31/05